January 15, 2004

Richard Balcomb
Head, Toxicology and Environmental Assessments
Ciba Specialty Chemicals
540 White Plains Road
Tarrytown, NY 10591

Dear Mr. Balcomb:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Thiodiethylene bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate) posted on the ChemRTK HPV Challenge Program Web site on August 28, 2003. I commend Ciba Specialty Chemicals for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Ciba advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Thiodiethylene bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate)

Summary of EPA Comments

The sponsor, Ciba Specialty Chemicals Corporation, submitted a test plan and robust summaries to EPA for thiodiethylene bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate), CAS No. 41484-35-9, dated August 8, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 28, 2003.

EPA reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. Adequate data were provided for boiling point, vapor pressure, and partition coefficient for the purposes of the HPV Challenge Program. The submitter needs to indicate whether the melting point is measured or estimated. In addition, any information verifying whether the water solubility is greater or less than 0.001 mg/L would assist in determining whether chronic aquatic toxicity testing is feasible.

2. Environmental Fate. Adequate data were provided for photodegradation and biodegradation for the purposes of the HPV Challenge Program. The submitter needs to provide a more detailed explanation regarding the hydrolysis of this chemical. In addition, the submitter needs to provide the input values used for the fugacity model calculations.

3. Health Effects. Adequate data were provided for the acute, repeated-dose, and reproductive toxicity endpoints for the purposes of the HPV Challenge Program. EPA reserves judgment on the mutagenicity data pending additional information in the robust summary. The chromosomal aberrations data are inadequate. To address the developmental toxicity endpoint, EPA recommends that the submitter conduct a combined reproductive/developmental toxicity screening test rather than the proposed teratogenicity test.

4. Ecological Effects. The acute aquatic toxicity tests are inadequate because all tests were conducted above the reported non-definitive water solubility value. Furthermore, EPA expects that the chemical is more likely to pose chronic than acute aquatic hazards. EPA reserves judgment, however, about whether to recommend a chronic test pending receipt of information to assist in determining whether the water solubility value is greater or less than 0.001 mg/L.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Thiodiethylene Bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate) Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for boiling point, vapor pressure, and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Melting point. The submitter needs to state whether the melting point is measured or calculated. If the data came from a reliable published source, the submitter needs to provide the name of the source.

Water Solubility. The "measured" water solubility of < 1mg/L is of limited use in deciding whether to conduct chronic aquatic toxicity testing. The submitter needs to provide more information, if available, to determine whether the measured water solubility is greater or less than 0.001 mg/L.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation and biodegradation are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submitter indicates that this chemical is extremely insoluble in water, and that it is likely to be stable in water. The submitter needs to provide a technical discussion explaining clearly the reasons for the asserted stability.

Fugacity. The submitter needs to provide the input values used for the fugacity model calculations in the robust summary.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data were provided for the acute, repeated-dose, and reproductive toxicity endpoints for the purposes of the HPV Challenge Program. EPA reserves judgment on the mutagenicity data pending the receipt of additional information. The data submitted for chromosomal aberrations are inadequate. EPA recommends that the submitter conduct a combined reproductive/developmental toxicity test according to OECD TG 421.

Acute Toxicity. Data submitted for acute dermal and inhalation toxicity need to be deleted from the test plan Summary Table (page 5) because the robust summaries characterized these studies as invalid (Klimisch code 3).

Genetic Toxicity (Gene Mutations). EPA reserves judgment on the gene mutation endpoint. Although the bacterial reverse mutation assay was conducted according to a protocol that is the basis for OECD TG 471, the submitter needs to provide more details in the robust summary to verify that the data are acceptable.

Genetic Toxicity (Chromosomal Aberrations). The"nuclear anomaly test" is not adequate for the purposes of the HPV Program. If no other data are available for this endpoint, EPA recommends that the submitter conduct an *in vitro* cytogenetics assay (e.g., OECD TG 473) to satisfy the test for chromosomal aberrations.

Reproductive Toxicity. This endpoint will be addressed with the reproductive organ weight and histopathology findings from the repeated-dose studies and data from a combined reproductive/developmental toxicity screening test (OECD TG 421).

Developmental Toxicity. To address this endpoint, EPA recommends that the submitter conduct a combined reproductive/developmental toxicity test (OECD TG 421) as indicated in HPV Challenge Program guidance rather than the proposed teratogenicity test (OECD TG 414).

Ecological Effects (fish, invertebrates, and algae)

The acute toxicity tests were considered inadequate because all tests were conducted above the reported non-definitive measured water solubility limit. However, EPA reserves judgement on the need for chronic toxicity tests depending on whether a more definitive measured water solubility value can be provided (see comments under physicochemical properties). No further testing is necessary if the submitter can more clearly document that the measured water solubility value is $\leq$0.001 mg/L.

If the water solubility is greater than 0.001 mg/L, EPA recommends chronic testing using either a 90-day rainbow trout early life stage test or a chronic invertebrate test, depending on which type of organism is determined to be more sensitive to this chemical. Generally, fish are more sensitive than invertebrates to phenolic compounds. However, the results of the invertebrate tests are inconclusive for this chemical. The test that used solvents resulted in toxicity at doses lower than the fish toxic doses, but the test that used ultrasound and filtering showed no toxicity at a limit concentration of 100 mg/L. It is possible that the toxicity observed in the test using solvents may have been due to the physical presence of the undissolved test substance rather than the intrinsic chemical toxicity of the substance. If possible, the submitter needs to comment on whether the toxicity observed in the first test was due to physical toxicity.

More information on EPA's response to related chemicals can be found in the Rubber and Plastic Additives (RAPA) Panel Consortium of the American Chemistry Council test plan and robust summaries to EPA for the Hindered Phenols Category dated December 18, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 15, 2002.

Specific Comments on the Robust Summaries

Health Effects

Genetic Toxicity. The robust summary for the reverse mutation assay in *Salmonella typhimurium* was missing information needed to evaluate the study including the number of replicates, frequency of dosing, treatment of positive and negative controls, whether or not a solvent was used, and the criteria for evaluating the results.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.